

Patent Application 09/417,175  
Attorney Docket No. PC10139A

### **REMARKS**

Claims 1, 7 - 10, 12 and 14 - 20 are now pending in the application. Claims 1 and 17 are currently amended. Claims 7, 8, 12, 15 and 17 were previously amended. Claims 2-6, 11 and 13 were previously canceled. Claims 9, 10, 14, 16, 18 and 19 are original. Claim 20 was previously added. A copy of the claims now pending in the application showing changes made to currently amended claims in accord with 37 CFR 1.121, as revised, has been provided.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein and the remarks below, applicants respectfully request reconsideration and withdrawal of the rejection set forth in the August 26, 2003 Office Action.

#### **Rejection under 35 USC § 103(a)**

In the Office Action, the Examiner maintained his rejection of claims 1, 7 - 10, 12 and 14 - 20 under 35 USC § 103(a) as "unpatentable over Doogan et al. (U.S. 4,962,128) in view of Howard et al. (U.S. 5,597,826) and Johnson (EP768083)." However, in the aforementioned final rejection the Examiner withdrew the Johnson reference from the rejection (see page 6, 4<sup>th</sup> line) and has chosen to rely solely on Doogan in view of Howard. Applicants will therefore direct their comments to this combination of references.

Applicants respectfully submit that the Examiner in his "Response to Argument" summary of applicants' arguments has overlooked key parts of their arguments. For example, the Examiner has apparently overlooked the fact that the Howard secondary reference refers only to pharmaceutical preparations containing two active components: (a) 5-HT reuptake inhibitors, of which sertraline is a preferred species, and (b) an unspecified compound from the genus of compounds represented by Howard's formula I. (The applicants respectfully refer the Examiner to the abstract, col. 1, line 6, to col. 24, line 58, of the specification, and the claims, especially claim 1 at col. 64, lines 49 - 55). Applicants submit that the teachings of Howard are directed to such combination formulations and are not directed to pharmaceutical formulations in which the only active ingredient is sertraline hydrochloride.

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Notwithstanding the above arguments, and in the interests of facilitating prosecution and for the sake of clarity, applicants have currently amended claim 1 without *pr* judice to recite:

“A pharmaceutical composition which comprises:

an essentially nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride for oral administration comprising about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride and ethanol and glycerin in an amount of about 8 to about 50% ethanol by weight in glycerin.”

In the first point set forth in the rejection, the Examiner asserts: “...Doogan et al. does teach the composition contains sertraline or its pharmaceutically acceptable salt, flavoring agents, and diluents, such as ethanol, glycerin and various like combinations thereof; also, the secondary Howard et al. reference to supplement the primary reference does disclose that liquid preparations containing sertraline may be prepared by conventional means with pharmaceutically acceptable additives such as non-aqueous vehicles (see col. 22, lines 47-55).”

Applicants respectfully submit that Doogan teaches diluents such as ethanol and glycerin within “...aqueous suspensions and/or elixirs ...” Applicants respectfully refer the Examiner to Dorland’s Illustrated Medical Dictionary, 25<sup>th</sup> edition, (publ. W. B. Saunders) where on page 125 the definition of the term “aqueous” is given as “watery; prepared with water.” Applicants further respectfully note that those skilled in the art will recognize that when the term “aqueous” is used to describe a liquid preparation, the liquid in the preparation is primarily water. Therefore, Doogan’s recital of ethanol and glycerin are within the context of diluents used with a liquid preparation wherein the liquid is primarily water. Applicants also submit that Doogan makes no specific reference to a liquid formulation containing sertraline hydrochloride.

The Examiner has invoked Howard et al., who teach pharmaceutical formulations with two active ingredients, as a secondary reference, thus implicitly conceding that Doogan by itself neither teaches nor suggests the pharmaceutical composition of instant claim 1. The Examiner cites col. 22, lines 47-55, of the Howard reference which beginning at col. 22, line 47, and continuing to line 57, recites:

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"Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid)."

Applicants respectfully submit that the Examiner has relied on teachings in Howard that do not refer to pharmaceutical preparations in which the sole active ingredient is sertraline, let alone sertraline hydrochloride specifically, but rather compositions containing (a) 5-HT reuptake inhibitors, of which sertraline is a preferred species, and (b) an unspecified compound from the genus of compounds represented by Howard's formula I. (The applicants respectfully refer the Examiner to the abstract, col. 1, line 6, to col. 24, line 58, of the specification, and the claims, especially claim 1 at col. 64, lines 49 - 55). In addition, Howard does not specifically refer to sertraline hydrochloride in connection any pharmaceutical formulation (see discussion of point 5, below). Applicants submit the presence of another complex chemical species in Howard's pharmaceutical composition is a disincentive to the skilled artisan seeking guidance in the preparation of "an essentially nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride" as this introduces complications regarding the solubility of sertraline hydrochloride.

The Examiner further states "it is well-known in the art that many liquid preparations of conventional means with pharmaceutically acceptable additives are available depending on the customer's choice." Applicants respectfully request clarification of the meaning of this sentence. Applicants respectfully submit that the Examiner errs if the Examiner is indicating that the availability of liquid pharmaceutical preparations in general make obvious the invention of a specific liquid pharmaceutical concentrate preparation designed to meet specific needs. Applicants respectfully submit that until a product based on the instant invention emerged on the market there has been

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no sertraline hydrochloride concentrate solution. The Examiner concludes: "Therefore, if the skillful artisan ... had desired to develop the product containing non-aqueous liquid concentrate compositions of sertraline, it would have been obvious for the skillful artisan in the art to have [been] motivated to incorporate Howard et al.'s non-aqueous vehicles into the Doogan et al. method because, for oral administration, Howard et al. does indicate that non-aqueous vehicles can be incorporated in the liquid preparations containing sertraline."

Applicants further submit that even if the artisan were to take the step of assuming that the other compound in Howard were absent, the Examiner's combination of Howard with Doogan does not produce the pharmaceutical composition of claim 1. Howard recites: "...non-aqueous *vehicles* (e.g. almond oil, oily esters or ethyl alcohol)..." but the term *vehicles*, especially within the context of a formulation having two active ingredients, may refer to a medium in which these ingredients are suspended rather than dissolved. In fact, Howard does not teach, suggest or hint at glycerin as a non-aqueous vehicle, let alone *the combination* of glycerin with ethanol as a *non-aqueous* vehicle. Applicants further submit that Doogan's diluents and any combination thereof are in the context of "*aqueous* suspensions and/or elixirs." The method of Doogan involves the use of water. Applicants further submit that the combined references do not teach, suggest or hint at the pharmaceutical preparation of currently amended claim 1 which recites "...an essentially nonaqueous, *filterable liquid concentrate solution* of sertraline hydrochloride ... comprising about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride and ethanol and glycerin". Further, neither reference teaches, suggests or hints at a *non-aqueous solvent* for sertraline hydrochloride that is a *combination* of ethanol and glycerin let alone a combination of "ethanol and glycerin in an amount of about 8 to about 50% ethanol by weight in glycerin" as recited in currently amended claim 1. In addition, neither Doogan nor Howard, either separately or in combination, hint at preparation of a sertraline hydrochloride *concentrate solution*. Neither reference refers specifically to sertraline hydrochloride in connection with a liquid preparation. Applicants respectfully submit that there is no motivation--indeed there is a disincentive--to combine Howard with Doogan, since Howard deals entirely with formulations containing more than one active ingredient,

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and even if Howard were combined with Doogan, the combination does not produce the sertraline hydrochloride concentrate solution of currently amended claim 1.

In the second point set forth in the Office Action, the Examiner states that Doogan teaches "that it is administered in dosages ranging from 50 - 500 mg/day." Applicants submit that the stated dosage level gives no indication of the concentration of sertraline hydrochloride attainable within a specific non-aqueous solvent system or what that solvent system should be. The aforesaid dosage refers only to oral or parenteral administration ( see col 2, line 18) and "can be carried out in both single and multiple dosages" (see col. 2, lines 29 - 30) and may employ any one of the many dosage forms listed at col. 2, lines 35 - 37, such as tablets. Applicants submit that "...a concentrate solution...for oral administration..." as recited in claim 1 is not among these dosage forms.

The Examiner also states that Doogan discloses at col. 2, lines 45 -46, that "the composition contains sertraline with concentration levels ranging from 0.5% to 90% by weight of the total compositions ... or its pharmaceutically acceptable salt, flavoring agents, and diluents such as ethanol, propylene glycol, and glycerin (see from col. 2 line 65 to col. 3, line 2). Applicants submit that the composition referred to at col. 2, lines 45 -46, may be any one of the many dosage forms listed at col. 2, lines 35 - 37, such as tablets. There is no reference to any liquid formulation specifically containing sertraline hydrochloride. There is no suggestion or indication that a binary non-aqueous solvent combination would lead to the filterable concentrate solution of instant claim 1, or any indication of the proportion of each solvent in said binary solvent combination that would lead to the filterable concentrate solution having the sertraline hydrochloride levels recited by instant claim 1.

Applicants submit that the diluents at col. 2, line 65, to col. 3, line 2, are directed to "aqueous suspensions and/or elixirs" (see col. 2, lines 63 - 64) and do not suggest or hint at the *non-aqueous* concentrate of claim 1.

The Examiner cites Howard as teaching "the dose of 0.3 mg to 10 mg per kg of body weight per day of the sertraline", at col. 23, lines 33 - 34. Applicants respectfully question the relevance of this teaching to instant claim 1 as currently amended. Applicants submit that (a) any pharmaceutical preparation will be directed to delivering

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an effective dose of the medication contained therein, as this is the purpose of a pharmaceutical preparation, (b) the recital of dose levels for sertraline in Howard does not teach or suggest the non-aqueous solvent combination or the proportions of said solvents required to make the concentrate solution of claim 1 or the quantities of sertraline hydrochloride that may be dissolved therein, and (c) the dosage range cited by the Examiner is for a 5-HT reuptake inhibitor that is preferably sertraline *administered in combination* with "preferably ... 0.1 mg to about 3 mg. per kg. of body weight per day of a compound of formula I ..." (see col. 23, lines 25 - 40, especially lines 36 - 38); therefore this dose level may not apply when Howard's compound of formula 1 is absent as in the instant invention. In addition, there is no specific reference to sertraline hydrochloride. The Examiner states: "...it would have been obvious for the skillful artisan ... to have [been] motivated to incorporate Howard et al.'s non-aqueous vehicles into the Doogan et al. method, thereby ascertaining the claimed dose by routine experimentation."

Applicants submit that because Howard has tailored his teachings to a pharmaceutical preparation containing a 5-HT reuptake inhibitor that may preferably be sertraline plus another active ingredient selected from a genus of compounds represented by Howard's formula 1, the skilled artisan would not be motivated to combine Howard with Doogan. Indeed, the constant presence of another active ingredient would be a disincentive to such a combination.

Applicants further respectfully submit that the Examiner has confused the term "dose" with the quantity of material dissolved in the concentrate solution of instant claim 1. At any given sertraline hydrochloride concentration, the dose delivered will depend on the volume of solution delivered. Claim 1 recites concentrations of sertraline hydrochloride, not doses. The instant invention provides a concentrated solution of sertraline hydrochloride, so that an appropriate dose may be contained in a small volume of said solution, which, as recited in the specification, can be dispersed in a relatively large volume of a beverage. Applicants submit that disclosure of the dosages of sertraline that may be administered in any of many dosage forms such as tablets is not the disclosure of the solubility of sertraline hydrochloride in a non-aqueous solvent or a combination of non-aqueous solvents.

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As discussed above, applicants submit that even if Howard were combined with Doogan in the manner suggested by the Examiner, the sertraline hydrochloride concentrate solution of currently amended claim 1 would not be produced. Indeed, the Examiner's statement "...thereby ascertaining the claimed dose by routine experimentation" appears to concede the point that the mere combination of Howard with Doogan is not enough to produce the concentrate solution of claim 1 since further experimentation would be required. Applicants submit that currently amended claim 1 is therefore unobvious over the cited references under 35 USC §103(a). Applicants further submit that the Examiner's concession that "routine experimentation" would be required after combination of Howard with Doogan in the manner suggested by the Examiner, does not render the instant invention as recited in claim 1 unpatentable under 35 USC §103(a), which recites "[p]atentability shall not be negatived by the manner in which the invention was made."

The Examiner further asserts "the filterable liquid concentration of the sertraline is naturally obtained as a result of the process, but is unrelated to the novelty; this does not add any patentable weight over the prior art reference." Applicants submit that the filterable property of the concentrate solutions of the instant invention distinguish them from liquid preparations such as suspensions having sertraline hydrochloride within the concentration range of instant claim 1 but in which the sertraline is only partially dissolved and in which particles of sertraline hydrochloride are present. None of the cited art separately or in the combination cited by the Examiner teaches or hints at "an essentially nonaqueous, filterable liquid concentrate solution" having a sertraline hydrochloride concentration of "18 mg/ml to about 78 mg/ml of sertraline hydrochloride".

In the third point the Examiner has withdrawn the Johnson reference.

In the fourth point the Examiner states "... applicants' argument of unexpected results can not take the place of evidence in the record." Applicants submit that the evidence is in the record, and respectfully refer the Examiner to the Examples in the specification where Example 4 recites 1 - 17 mg of sertraline hydrochloride dissolves in 1 ml of ethanol and Example 5 recites 1 - 78 mg of sertraline hydrochloride in 1 ml of a nonaqueous solution containing ethanol and glycerin.

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Applicants note that the maximum level attained with the combination of ethanol and glycerin is almost 5 times greater than that attained with the use of ethanol alone. Applicants submit that the dramatic increase in sertraline hydrochloride concentration range and maximum concentration in the binary ethanol-glycerin solution is surprising and unexpected compared to the result obtained with ethanol alone.

Applicants further submit that the surprising concentration levels attainable with the nonaqueous filterable liquid concentrate solutions of claim 1 have the practical and commercially important consequence of enabling the preparation of a range of dosage levels, including the preferred level of about 22.4 mg/ml of sertraline hydrochloride which is equivalent to about 20 mg/ml of sertraline (see pages 5 and 7 of the instant specification) and is not attainable with ethanol alone. This enables the dispersal of a small concentrated dose of sertraline hydrochloride in relatively large quantity of beverage to facilitate administration of this medication as recited in the specification.

In his fifth point, the Examiner states: "However there is a motivation to combine the references. Doogan et al. do disclose the pharmaceutical composition containing sertraline hydrochloride (see col. 1, line 68) with a dose from 25 mg to 200 mg for treating anxiety-related disorders (see col. 2, lines 20 -23)." Applicants submit that Doogan at col. 1, line 68, lists examples of "pharmaceutically acceptable salts of sertraline that can be used to treat anxiety-related disorders" but does not disclose a pharmaceutical composition. Applicants further submit that Doogan recites at col. 2, lines 16-21, "Sertraline or a pharmaceutically acceptable salt thereof, when used to treat anxiety-related disorders, may be administered either orally or parenterally. It is generally administered in dosages ranging from 50 - 500 mg per day when used to treat obsessive compulsive disorder, and from about 25-500 mg per day when used to treat other anxiety-related disorders," Applicants submit there is no specific reference to the sertraline hydrochloride salt. The dosage to which the Examiner refers is to sertraline itself or any one of 13 sertraline salts. Moreover, applicants respectfully submit that the Examiner has confused the term dosage with the concentration of sertraline hydrochloride in solution. The Examiner refers to Doogan col. 2, line 65 to col. 3, line 2 as listing diluents. The diluents listed also include water and the diluents refer to "aqueous suspensions and/or elixirs" (col. 2, lines 63-64) but not a "nonaqueous concentrate solution" as recited in claim 1. Applicants submit that



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the stated dosage range gives no indication of the concentration of sertraline hydrochloride itself that is attainable within a specific non-aqueous solvent system or what that solvent system should be. The aforesaid dosage refers only to oral or parenteral administration (see col 2, line 18) and "can be carried out in both single and multiple dosages" (see col. 2, lines 29 - 30) and may employ any one of the many dosage forms listed at col. 2, lines 35 - 37, such as tablets. Applicants submit: "...a concentrate solution...for oral administration..." as recited in claim 1 is not among these dosage forms.

The Examiner states: "Howard et al. discloses expressly the pharmaceutical composition containing sertraline hydrochloride (see col. 20, line 31) with a dose of from 0.1 mg to 200 mg (see col. 24, lines 7-8), ...non-aqueous vehicles such as ethyl alcohol...." Applicants submit that while Howard at col. 20, line 31, refers to sertraline hydrochloride the reference to sertraline hydrochloride at Howard, col. 24, lines 7-8, is in error as the doses recited therein refer to the genus of compounds of formula I (see col. 24, line 3). Applicants further submit that contrary to the Examiner's assertion, sertraline hydrochloride itself is never "expressly" disclosed in any of the pharmaceutical compositions described in Howard.

Applicants further submit that Howard at col. 20, lines 63-66, refers to "[t]hose compounds of the formula I which are also acidic in nature ... are capable of forming base salts with various pharmacologically acceptable cations." Applicants submit that such compounds of formula I due to the basic nature of sertraline or the cationic nature of a sertraline salt can interact with sertraline or a sertraline salt with the possible formation of insoluble residues. Applicants submit that Howard has tailored his teachings to a pharmaceutical preparation that always contains (a) a 5-HT reuptake inhibitor, preferably sertraline, or a salt thereof, but not specifically sertraline hydrochloride and (b) another compound selected from the genus of compounds represented by Howard's formula I which can interact with sertraline or a salt thereof. Applicants submit that the skilled artisan would not be motivated to combine Howard with Doogan, since the constant presence of another active ingredient that can cause complications and the lack of teachings specifically related to sertraline hydrochloride would be a disincentive to such a combination.

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The Examiner refers to col. 22, lines 51-56, of Howard which discloses components that may be used in compositions containing the aforementioned two active components. As the composition of instant claim 1 recites a “nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride ... ethanol and glycerin in an amount of about 8 to about 50% ethanol by weight in glycerin,” Howard’s teaching of suspending agents is irrelevant and the teaching of non-aqueous “vehicles” such as ethyl alcohol does not indicate whether the vehicle produces a suspension, a solution or a combination of suspension and solution, and does not teach or suggest a concentrate solution, let alone the binary solvent system as recited in instant claim 1. There is no specific mention of sertraline hydrochloride or of a composition whose only active ingredient is sertraline hydrochloride in any of these disclosures. The Examiner’s reference to Howard’s teaching of methanesulfonate is not relevant as this refers to Howard’s compounds of formula I, and none of the instant current claims refer to methanesulfonate.

The Examiner appears to assert that both Doogan and Howard definitively deal with pharmaceutical compositions containing “sertraline hydrochloride”. Applicants submit that, contrary to this, Doogan does not specifically refer to sertraline hydrochloride in connection with any liquid preparation and Howard never specifically refers to sertraline hydrochloride in connection with any preparation. Furthermore, the Examiner confuses “dose” with the concentration of an ingredient in solution. Contrary to the assertion of the Examiner, neither reference specifically refers to sertraline hydrochloride in a liquid preparation, let alone a nonaqueous solution concentrate.

The Examiner describes the skillful artisan as being motivated to combine Howard’s methanesulfonate “into the Doogan et al. pharmaceutical composition containing sertraline hydrochloride ....” Applicants respectfully submit there is no motivation whatsoever for this combination as Howard refers to methanesulfonate only with regard to the genus of compounds of formula I, methanesulfonate is not recited in the instant current claims, and Doogan never specifically recites sertraline hydrochloride in any liquid preparation.

Applicants further submit that even if the references were to be combined in the manner described by the Examiner, the Examiner concedes that even after such combination the skilled artisan would need to perform “routine experimentations” “to

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achieve the non-aqueous liquid concentrate having the unique amounts and combination of excipients ....” Applicants respectfully submit that the Examiner has conceded that the amounts and combination of excipients of the non-aqueous liquid concentrate of instant claim 1 are “unique” and cannot be arrived at without further “routine experimentation”. Applicants submit that the Examiner has conceded that the concentrate solution of instant claim 1 is therefore unobvious over the references combined in the manner suggested by the Examiner, as the amounts and composition are “unique” and must be arrived at by “routine experimentation”. Applicants submit that 35 USC §103(a), recites, in pertinent part: “Patentability shall not be negated by the manner in which the invention was made.” Applicants request allowance of instant currently amended claim 1 since even if the manner by which the “unique” composition of instant claim 1 was achieved was “routine experimentation” it is patentable under 35 USC §103(a).

Applicants further respectfully submit that a non-aqueous sertraline hydrochloride concentrate solution based on the instant claims is currently being sold to meet the needs of patients who are non-compliant with treatment because they “...dislike or have difficulty swallowing tablets or capsules...” (see page 3 line 24 - page 4, line 2). The applicants submit that the instant invention provides a technical solution to this problem in the form of the instant nonaqueous oral concentrate solution which permits the dispersal of the appropriate dose, contained in a very small volume of concentrate solution, in a large volume of a beverage having an acceptable taste. (See page 8, line 30, to page 9, line 7, of the instant specification.). Applicants submit that the commercial product based on the instant claims meets a long-felt need, and that the instant claims are therefore patentable under 35 USC §103(a), and respectfully request withdrawal of the rejection and solicit allowance of these claims.

For all of the foregoing reasons applicants submit that instant claim 1, as currently amended, is patentable under 35 USC §103(a) over the cited references, either separately or in the combination cited by the Examiner, and respectfully request withdrawal of the rejection. Applicants further submit that claims 7-10, 12, 14-16, 17 as currently amended, and 18 -20 all of which incorporate the novel and unobvious features of claim 1, are all patentable under 35 USC §103(a) over the cited references, either separately or

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in the combination cited by the Examiner, and respectfully request withdrawal of the rejection.

**Rejection under 35 USC §112, first paragraph**

The Examiner rejected claims 15 and 17 under 35 USC §112, first paragraph, as directed to a method "for preventing and treating diseases, such as cancers" for lack of enablement. Claim 15 recites, in relevant part: "A method of treating or preventing diseases or conditions which are caused by disorders of the serotonergic system..." but does not recite cancer. Applicants respectfully submit that the rejection of claim 15 under 35 USC §112 is erroneous, and respectfully request withdrawal of the rejection.

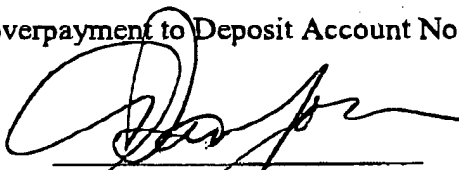
Without prejudice and in the interests of facilitating prosecution, applicants have amended claim 17 by deletion of the term "cancer".

Applicants respectfully submit that previously amended claim 15 and currently amended claim 17 are patentable under 35 USC §112, first paragraph, and respectfully request withdrawal of the rejection.

In view of the amendments set forth herein and remarks above, the applicants respectfully submit that the pending claims are fully allowable, and solicits the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

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